

# Clinical comparison of dexmedetomidine and medetomidine for isoflurane balanced anaesthesia in horses

## Abstract

**Objective** To compare the effects of two balanced anaesthetic protocols (isoflurane – dexmedetomidine vs. medetomidine) on sedation, cardiopulmonary function and recovery in horses.

**Study design** Prospective, blinded, randomised clinical study.

**Animals** Sixty healthy adult warm blood horses undergoing elective surgery.

**Methods** Thirty horses each were sedated with dexmedetomidine  $3.5 \mu\text{g kg}^{-1}$  (group DEX) or medetomidine  $7 \mu\text{g kg}^{-1}$  (group MED) intravenously. After assessing and topping up sedation if necessary, anaesthesia was induced with ketamine/diazepam and maintained with isoflurane in oxygen/air and dexmedetomidine  $1.75 \mu\text{g kg}^{-1} \text{ hour}^{-1}$  or medetomidine  $3.5 \mu\text{g kg}^{-1} \text{ hour}^{-1}$ . Ringer's lactate ( $7\text{--}10 \text{ mL kg}^{-1} \text{ hour}^{-1}$ ) and dobutamine were administered to maintain normotension. Controlled mechanical ventilation maintained end-tidal expired carbon dioxide pressures at  $40\text{--}50 \text{ mmHg}$  ( $5.3\text{--}6.7 \text{ kPa}$ ). Heart rate, invasive arterial blood pressure, inspired and expired gas composition and arterial blood gases were measured. Dexmedetomidine  $1 \mu\text{g kg}^{-1}$  or medetomidine  $2 \mu\text{g kg}^{-1}$  were applied for timed and scored recovery phase. Data were analysed using two-way repeated-measures analysis of variance (ANOVA) and chi-squared test. Significance was considered when  $p \leq 0.05$ .

**Results** In group DEX, significantly more horses ( $n = 18$ ) did not fulfil sedation criteria prior to induction and received one or more top-ups, whereas in group MED only two horses

needed one additional bolus. Median total sedation doses (range) were dexmedetomidine 4  $\mu\text{g kg}^{-1}$  (3.5–9) or medetomidine 7  $\mu\text{g kg}^{-1}$  (7–9). During general anaesthesia, cardiopulmonary parameters did not differ significantly between groups. Recovery scores in group DEX were significantly better than in group MED.

## **Conclusion and clinical relevance**

Horses receiving dexmedetomidine required more than 50% medetomidine dose to reach equivalent sedation. During isoflurane anaesthesia, cardiopulmonary function was comparable between the two groups. Recovery scores following dexmedetomidine were better compared to medetomidine.

## Introduction

A balanced anaesthetic protocol with partial intravenous anaesthesia (PIVA) using two or more ancillary agents is a common concept in modern equine general anaesthesia (Gozalo-Marcilla et al. 2014, 2015). It allows reducing the amount of volatile agents and therefore keeps undesirable effects to a minimum. Constant rate infusions (CRIs) of different  $\alpha_2$ -adrenergic agonists in combination with isoflurane have been used in anaesthetised horses for this purpose (Ringer et al. 2007; Devisscher et al. 2010; Schauvliege et al. 2011; Marcilla et al. 2012; Pöppel et al. 2015). Furthermore, the analgesic effects of these drugs can improve recovery qualities (Bettschart-Wolfensberger & Larenza 2007; Gozalo-Marcilla et al. 2015).

Medetomidine, a highly selective, short acting  $\alpha_2$ -adrenergic agonist [selectivity ratio ( $\alpha_2:\alpha_1$ ) 1620:1] (Virtanen et al. 1988) has been shown to reduce the minimum alveolar concentration (MAC) of isoflurane and to provide rapid recoveries of good quality in ponies and horses (Bettschart-Wolfensberger et al. 2001; Ringer et al. 2007). Classic side effects of  $\alpha_2$ -adrenergic agonists including bradycardia, arrhythmias, decreases in cardiac output and increases in systemic vascular resistance have been documented for medetomidine (Bettschart-Wolfensberger et al. 1999a; Yamashita et al. 2000; Grimsrud et al. 2012). Compared to a CRI, more prominent side effects were described following an intravenous (IV) bolus (Bettschart-Wolfensberger et al. 1999a). However, within 30 minutes, when steady state conditions of medetomidine plasma levels were achieved (Bettschart-Wolfensberger et al. 1999b), an improvement of cardiopulmonary variables was demonstrated. Therefore, it was concluded that the infusion of  $3.5 \mu\text{g kg}^{-1} \text{ hour}^{-1}$  causes minimum cardiopulmonary depression, once the effects of a  $5 \mu\text{g kg}^{-1}$  bolus have waned (Bettschart-Wolfensberger et al. 1999a).

A bolus of dexmedetomidine, the dextro-rotary and active enantiomer of medetomidine, showed a large volume of distribution at steady-state with a rapid clearance, resulting in a shorter plasma elimination half-life than medetomidine in horses (8 minutes for

dexmedetomidine 10  $\mu\text{g kg}^{-1}$  vs. 29 minutes for medetomidine 5  $\mu\text{g kg}^{-1}$ ) (Grimsrud et al. 2012; Rezende et al. 2015). A dexmedetomidine bolus has also shorter lasting cardiopulmonary effects without a decrease in heart rate (HR) compared to medetomidine (Bettschart-Wolfensberger et al. 1999b, 2005). The use of a dexmedetomidine CRI at a rate of 1.75  $\mu\text{g kg}^{-1} \text{ hour}^{-1}$  in isoflurane anaesthetised horses under clinical circumstances produced limited cardiopulmonary effects, improving recovery qualities significantly (Marcilla et al. 2012).

Preliminary studies in horses by Bettschart-Wolfensberger et al. (2005) showed that medetomidine 7  $\mu\text{g kg}^{-1}$  had equivalent sedative effects to dexmedetomidine 3.5  $\mu\text{g kg}^{-1}$ .

Direct comparative clinical studies with dexmedetomidine at a 50% dose of medetomidine have been conducted in dogs (Granholm et al. 2007; Raszplewicz et al. 2013) and sheep (Kästner et al. 2001).

The main purpose of the study was to compare two different PIVA protocols (isoflurane with either dexmedetomidine or medetomidine) in horses undergoing elective surgeries to assess the effects on sedation, cardiopulmonary parameters and recovery phase. The hypothesis of our study was that the sedation doses were expected to be similarly potent, with no unexpected side effects after either dexmedetomidine or medetomidine bolus. Moreover, based on the available pharmacokinetic data and previous clinical reports, fewer and shorter lasting cardiopulmonary effects with a lower incidence of partial pressure of oxygen ( $\text{PaO}_2$ ) < 80 mmHg (10.7 kPa) were hypothesised during dexmedetomidine CRI compared with medetomidine in isoflurane-anaesthetised horses. Safe recoveries were expected with both of the drugs.

## **Material and methods**

### **Study design and animals**

This prospective randomised blinded clinical study was performed with the ethical approval of the local committee for animal experimentation (*removed for blinding*). Written owners' consent was obtained.

Sixty client-owned, non-food producing horses of various breeds presented for elective surgeries were included in the study. Inclusion criteria were body weight ( $\geq 200$  kg), age (2–20 years), physical status ASA (American Society of Anaesthesiologists) 1 or 2 based on a physical examination, and procedure type (no surgery of the head region, no rope-assisted recovery required). Food but not water was withheld for 10–16 hours prior to anaesthesia. Each patient was randomly assigned to either group DEX (dexmedetomidine) or MED (medetomidine) at the beginning of the experiment, using previously prepared opaque envelopes opened by a person who was not involved in the study. Demographic data and body condition score (BCS) were recorded on a separate data sheet, BCS adapted from Carroll & Huntington 1988. All anaesthetic procedures were performed by the same experienced anaesthetist, who was unaware of the treatment at any time until the end of the study, including the recovery phase.

### **Study protocol**

Sixty minutes prior to sedation, a jugular catheter was placed following desensitisation of the insertion site with 4 mL of mepivacaine 2% (*removed for blinding*). The horses received either cefquinome 1 mg kg<sup>-1</sup> IV (*removed for blinding*) or a combination of sodium benzylpenicillin 30,000 I.E. kg<sup>-1</sup> (*removed for blinding*) and gentamicin 9 mg kg<sup>-1</sup> IV (*removed for blinding*) as antibiotherapy and flunixin meglumine 1.1 mg kg<sup>-1</sup> IV (*removed for blinding*) for soft tissue surgeries or phenylbutazone 4 mg kg<sup>-1</sup> IV (*removed for blinding*) for orthopaedic surgeries as anti-inflammatory drugs.

Each horse was premedicated with acepromazine 0.03 mg kg<sup>-1</sup> (*removed for blinding*) intramuscularly (IM) 30 minutes prior to the start of the study. Immediately before induction

of anaesthesia, horses were sedated with dexmedetomidine  $3.5 \mu\text{g kg}^{-1}$  IV (*removed for blinding*) or medetomidine  $7 \mu\text{g kg}^{-1}$  (*removed for blinding*) IV, depending on group allocation. Medication was prepared by a veterinarian not involved in the study and diluted with sodium chloride to a total volume of 20 mL and 5 mL for sedation and top-ups, respectively. One-third of the dose was administered as a bolus in the stable, then the mouth was rinsed and the horse walked into the induction area, where the remaining two-thirds were injected slowly over 2 minutes. Five minutes later, depth of sedation was assessed and considered adequate when the criteria listed in Table 1, adapted from Taylor et al. (2014), were fulfilled. If one or more conditions were not present, a top-up of dexmedetomidine  $0.5 \mu\text{g kg}^{-1}$  or medetomidine  $1 \mu\text{g kg}^{-1}$  was administered IV, depending on group allocation. Sedation was re-evaluated after 3 minutes. This procedure was repeated once more if necessary. If sedation remained insufficient, a third extra bolus of dexmedetomidine  $1 \mu\text{g kg}^{-1}$  or medetomidine  $2 \mu\text{g kg}^{-1}$  was given IV over 2 minutes to ensure a good level of sedation prior to anaesthesia induction. The time needed for bolus application and until induction of anaesthesia as well as the total amount of required sedation were recorded.

Anaesthesia was induced with diazepam  $0.02 \text{ mg kg}^{-1}$  IV (*removed for blinding*) and ketamine  $2.2 \text{ mg kg}^{-1}$  (*removed for blinding*) mixed in one syringe. This was considered as anaesthesia time point zero ( $t_0$ ). Once the horses were recumbent and the tracheas intubated (silicone tubes, I.D. 22 to 30 mm), they were hoisted onto a padded surgery table and attached to a large animal circle system (*removed for blinding*). Controlled mechanical ventilation (CMV) of the lungs was commenced immediately to maintain end-tidal expired carbon dioxide pressures ( $\text{PE}'\text{CO}_2$ ) of 40–50 mmHg (5.3–6.7 kPa). Anaesthesia was maintained using isoflurane (*removed for blinding*) delivered in oxygen and air [fraction of inspired oxygen ( $\text{F}_\text{I}\text{O}_2$ ) between 0.45–0.55]. Every 5 minutes, depth of anaesthesia and isoflurane supply was assessed and readjusted subjectively by the main investigator, unaware of the treatment, based on clinical parameters. Dexmedetomidine  $3.5 \mu\text{g kg}^{-1} \text{ hour}^{-1}$  or

medetomidine  $7 \mu\text{g kg}^{-1} \text{ hour}^{-1}$  for group DEX and MED, respectively, were started immediately after positioning the animal on the surgery table, delivered IV by an infusion pump (*removed for blinding*). Direct measurement of MAP and collection of arterial blood samples were performed via a catheter inserted into the facial artery. The catheter was linked to a pressure transducer, placed at the level of the heart with the scapulohumeral joint as a reference point and zeroed to ambient pressure. Heart rate, MAP,  $\text{FiO}_2$ ,  $\text{PE}'\text{CO}_2$  and  $\text{ET}'\text{Iso}$  were recorded every 5 minutes. Dobutamine up to  $1.25 \mu\text{g kg}^{-1} \text{ minute}^{-1}$  (*removed for blinding*), administered by an infusion pump (*removed for blinding*) and Ringer's lactated solution  $7\text{--}10 \text{ mL kg}^{-1} \text{ hour}^{-1}$  (*removed for blinding*) were given IV to maintain the mean arterial blood pressure (MAP)  $> 70 \text{ mmHg}$ . In order to keep the MAP values stable, the rate of dobutamine was minimally readjusted every 5 minutes based on a prepared rate scale in dependence on the MAP ( $60\text{--}64 \text{ mmHg}$ :  $1.25 \mu\text{g kg}^{-1} \text{ minute}^{-1}$ ;  $65\text{--}70$ :  $1$ ;  $71\text{--}75$ :  $0.8$ ;  $76\text{--}80$ :  $0.7$ ;  $81\text{--}85$ :  $0.5$ ;  $86\text{--}90$ :  $0.25$ ;  $> 90$ :  $0$ ). If the MAP remained below  $65 \text{ mmHg}$  or if the HR increased to a value higher than 1.5 times HR at  $t_{30}$ , a  $500 \text{ mL}$  IV bolus of hetastarch (*removed for blinding*) was given in addition to the dobutamine infusion. This bolus application was repeated every 5 minutes, until MAP was  $> 65 \text{ mmHg}$ . If nystagmus or incessant fighting against the ventilator occurred, ketamine  $0.1 \text{ mg kg}^{-1} \text{ IV}$  was administered. In case of sudden movement thiopental  $0.5\text{--}1 \text{ mg kg}^{-1} \text{ IV}$  (*removed for blinding*) was administered. At time points  $t_{30}$ ,  $t_{60}$ ,  $t_{90}$  and  $t_{150}$  arterial and venous blood samples were drawn anaerobically, using pre-heparinized syringes (*removed for blinding*) and analysed immediately (RAPIDPoint, Siemens, Germany). Analysis included pH, venous and arterial oxygen and carbon dioxide partial pressures ( $\text{PvCO}_2$ ,  $\text{PvO}_2$ ,  $\text{PaCO}_2$ ,  $\text{PaO}_2$ ), base excess (BE) and electrolytes ( $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{++}$ ,  $\text{Cl}^-$ ) as well as arterial lactate (Lac). Total haemoglobin of the arterial blood sample was measured separately (*removed for blinding*). If a  $\text{PaO}_2 < 80 \text{ mmHg}$  ( $10.7 \text{ kPa}$ ) was detected,  $\text{FiO}_2$  was changed to 1.0 and salbutamol  $2 \mu\text{g kg}^{-1}$  was administered intratracheally. These horses were excluded from further blood gas analysis. The ratio of

arterial partial pressure of oxygen to fraction of inspired oxygen ( $\text{PaO}_2/\text{FiO}_2$ ) was calculated later for  $t_{30}$ ,  $t_{60}$ ,  $t_{90}$  and  $t_{150}$  under exclusion of those horses with  $\text{FiO}_2 = 1.0$ .

Thirty minutes prior to the end of anaesthesia, morphine  $0.1 \text{ mg kg}^{-1}$  IM (*removed for blinding*) was administered. At the end, all infusions and CMV were stopped and horses were hoisted from the table and placed in a padded recovery box. From the moment of the lateral positioning of the horse, the recovery timing was started. Ventilation was assisted using a demand valve until the horses started to breathe spontaneously. Subsequently, dexmedetomidine  $1 \mu\text{g kg}^{-1}$  (group DEX) or medetomidine  $2 \mu\text{g kg}^{-1}$  (group MED) was administered IV slowly over 2 minutes. If horses either moved or showed excessive nystagmus and were in danger of an untimely recovery, the dose of either dexmedetomidine or medetomidine was doubled. Oxygen was administered ( $10 \text{ L minute}^{-1}$ ) through the endotracheal tube (ETT). The tracheas were extubated once the horses either started to show nystagmus or regained their swallow reflex. Before removing the ETT, 5 mL phenylephrine 0.15% drops (*removed for blinding*) were instilled into each nasal cavity. Horses were allowed to recover without assistance. Times required until extubation, first limb movement and time to attain sternal and standing positions were noted. The main anaesthetist assessed the recovery quality. It was graded on a standard scoring 5-point scale (Table 2) with a score of 1 representing the best recovery (Vettorato et al. 2010; Bettschart-Wolfensberger et al. 2011; Gozalo-Marcilla et al. 2012).

## Statistical analysis

Sample size calculations indicated, that 27 horses per group were necessary to show a statistically significant reduction from 50% to 15% incidence of horses with  $\text{PaO}_2$  of  $< 80 \text{ mmHg}$  ( $10.7 \text{ kPa}$ ). The average value of 50% incidence for that low  $\text{PaO}_2$  values in horses anaesthetised under similar conditions as in the present study was based on previous reports (Kalchofner et al. 2006; Ringer et al. 2007).



Data distribution was tested with the Kolmogorov-Smirnoff test of normality. Depending on normality, the *t*-test or the Mann-Whitney test were used to assess significant differences between groups in weight, age, anaesthesia duration, recovery times and scores. Repeatedly measured parameters were analysed using a two-way repeated- measures analysis of variance (ANOVA) for differences between groups and over time. Chi-squared test was used to evaluate significant group differences between required doses of sedation and intra-anaesthetically injected ketamine or thiopental. Significance was considered when  $p \leq 0.05$ . Statistical analysis was performed using SPSS 19 (*removed for blinding*) except for repeated-measures ANOVA tests that were performed with SigmaStat 3.5 (*removed for blinding*). Results of parametric data are expressed as mean  $\pm$  standard deviation (SD) and results of nonparametric data as median and (range).

## Results

Figure 1 shows the number of included and excluded horses per group throughout the entire study period. Six horses in DEX and four horses in MED were treated with salbutamol 2  $\mu\text{g kg}^{-1}$  intratracheally and  $\text{FIO}_2$  was set to 1.0. Partial pressure of  $\text{O}_2$  was  $> 80$  mmHg (10.7 kPa) 30 minutes after these interventions in all horses. One horse in group DEX was euthanized after 115 minutes due to bad prognosis for the intra-operatively detected orthopaedic problem, and was consequently not available for data analysis during recovery. Two horses in group MED were excluded from data analysis of the general anaesthesia, as one suffered from an incident of pulmonary air-embolism and one received atropine 6  $\mu\text{g kg}^{-1}$  IV. This was due to a HR of 15 bpm. Bradycardia resolved following atropine. In group MED, only the horse suffering from air-embolism was excluded from data analyses during the recovery, as in this case the study protocol could not be followed.

No significant differences in age (DEX:  $7.8 \pm 5.2$  years; MED:  $8 \pm 5.4$  years), body weight (DEX:  $534 \pm 88$  kg; MED:  $507 \pm 71$  kg), BCS, gender or type of recumbency were

identified. The total duration of anaesthesia was not different between groups (DEX:  $145 \pm 50.8$  minutes; MED:  $151 \pm 36$  minutes). In group DEX, a higher number of horses ( $n = 18$ ) did not fulfil the sedation criteria and needed one or more top-ups ( $p < 0.001$ ), whereas only two horses needed one additional bolus in group MED (Fig. 1). In group DEX seven horses did not meet sedation criteria after three top-ups following the protocol described. These horses were sedated slowly to effect with dexmedetomidine  $1 \mu\text{g kg}^{-1} \text{ minute}^{-1}$  until sedation was considered deep enough for induction of general anaesthesia. The median dose of sedation necessary to fulfil sedation criteria prior to anaesthesia induction was  $4 \mu\text{g kg}^{-1}$  (3.5–9) in group DEX and  $7 \mu\text{g kg}^{-1}$  (7–9) in group MED. The time from the start of sedation to induction of anaesthesia was longer in DEX with 15 (9.5–35) minutes compared to 11 (9.5–13) minutes in MED, respectively ( $p < 0.001$ ).

No significant difference was found between groups regarding mean  $\text{ET}'_{\text{Iso}}$  concentrations (Mean  $\pm$  SEM; DEX:  $1.2 \pm 0.02$  %, MED:  $1.1 \pm 0.02$  %,  $p = 0.36$ ). Nevertheless, group-independent changes over time were significant with  $\text{ET}'_{\text{Iso}}$  increasing over time compared to  $t_5$  ( $p < 0.001$ ). Figure 2 and Table 3 display cardiopulmonary parameters emphasising significant group differences of MAP at  $t_{15}$  ( $p = 0.009$ ) and  $t_{20}$  ( $p = 0.029$ ). A group-independent increase over time compared to  $t_5$  was found for HR ( $p < 0.001$ ) and a decrease over time for MAP ( $p < 0.001$ ).

There was no significant difference between the groups in the mean dobutamine infusion rate [DEX:  $0.6 \pm 0.2 \mu\text{g kg}^{-1} \text{ minute}^{-1}$ , MED:  $0.5 \pm 0.2 \mu\text{g kg}^{-1} \text{ minute}^{-1}$  ( $p = 0.76$ )]. An equal number of horses ( $n = 17$ ) in group DEX and MED required one or several boli of ketamine. Six horses in DEX and three horses in MED were given a single dose of 0.5 or 1  $\text{mg kg}^{-1}$  thiopental, either to allow intubation (four in DEX, three in MED) or due to limb or ear movement during surgery (two in DEX). Information about BE, pH, electrolytes, Lac and haemoglobin is given in Table 3.

All horses started to breathe spontaneously within 3–4 minutes after disconnection

from the breathing system, which timed the start of administration of the post sedation. Times related to recovery did not differ significantly between groups, with recorded time spans in minutes (range) as the following: time to extubation DEX: 14 (4–21), MED: 18 (3–20) ( $p = 0.12$ ); time to sternal recumbency: DEX 39 (0–77), MED: 38 (0–73) ( $p = 0.93$ ); time from sternal to standing DEX 22 (1–66), MED: 14 (0.5–63) ( $p = 0.22$ ); total time to standing DEX: 56 (26–118), MED: 58 (32–93) ( $p = 0.26$ ). Recovery scores were better with DEX (1 (1–4) compared to MED (2 (1–4)) ( $p = 0.042$ ) (Fig. 3). Four horses in DEX and one horse in MED were given an additional bolus of either dexmedetomidine or medetomidine for recovery (Fig. 1).

## Discussion

The results of the present study showed that horses receiving dexmedetomidine at 50% dose rate of medetomidine required more additional doses for sedation prior to anaesthesia induction than those receiving medetomidine. Cardiopulmonary function was maintained within clinically acceptable levels during general anaesthesia with both drugs. Moreover, recovery qualities were better in horses receiving dexmedetomidine.

In order to sedate the horses before induction of general anaesthesia, dexmedetomidine did not seem to be a reliable drug at the doses reported here. The sedation doses were chosen following the experimentally presumed equivalence of dexmedetomidine at 50% dose rate of medetomidine in dogs and sheep, as comparative studies in horses were lacking at the time of study design (Kuusela et al. 2000; Kästner et al. 2001; Granholm et al. 2007). By then, the only study available regarding dexmedetomidine, reported the dose used in the present study (Bettschart-Wolfensberger et al. 2005). Later on, other authors used  $3.5 \mu\text{g kg}^{-1}$  IV dexmedetomidine prior to anaesthesia induction and 27.5 % (Marcilla et al. 2012) or 60 % (Marly-Voquer et al. 2016) of horses needed additional sedation to achieve deep sedation, as considered necessary before ketamine anaesthesia induction by most authors.

The absence of deep sedation in many horses with the dose of dexmedetomidine used in this study questions the previously reported equipotency of dexmedetomidine 3.5  $\mu\text{g kg}^{-1}$  to medetomidine 7  $\mu\text{g kg}^{-1}$  in horses (Bettschart-Wolfensberger 2005). The aforementioned shorter plasma elimination time of dexmedetomidine compared to medetomidine may have contributed to this, as it could have led to plasma levels already falling beyond levels causing deep sedation in individual horses at time of sedation scoring, resulting in the higher number of dexmedetomidine top-ups (Grimsrud et al. 2012; Rezende et al. 2015). In awake horses receiving dexmedetomidine CRIs, a substantial inter-horse variation in pharmacokinetic parameters was observed, with remarkable differences in sedation levels directly related to plasma levels of dexmedetomidine (Ranheim et al. 2015). This is in contrast to the previously reported stable plasma levels of medetomidine (Bettschart-Wolfensberger et al. 1999b), which might offer further explanation of the cardiopulmonary and recovery quality – related differences observed between the two drugs.

For both drugs compared in this study, typical  $\alpha_2$ -adrenergic agonist associated cardiopulmonary effects were recorded following induction of anaesthesia (Bettschart-Wolfensberger et al. 1999a; Kuusela et al. 2000), but cardiopulmonary function remained within clinically acceptable limits using dobutamine CRI and fluid substitution. Despite the higher bolus doses for sedation with dexmedetomidine, MAP values at time points  $t_{15}$  and  $t_{20}$  were statistically significantly higher with medetomidine than with dexmedetomidine. This was probably a consequence of shorter plasma half-life of dexmedetomidine leading to quicker establishment of steady state plasma levels (Bettschart-Wolfensberger et al. 1999a; Grimsrud et al. 2012; Rezende et al. 2015) with minimal effect on cardiopulmonary function. Further studies comparing the plasma levels and pharmacokinetic profiles of the two drugs combined with ketamine and followed by isoflurane would be necessary, in order to evaluate the exact differences and the subsequent effects on the cardiopulmonary system.

No differences in ET'Iso were detected between groups and values were comparable with previous studies using the similar study designs (Kalchofner et al. 2009; Devisscher et al. 2010; Schauvliege et al. 2011; Marcilla et al. 2012). The clinical variables used here to assess anaesthetic depth are subjective and may have led to biased values of ET'Iso. Nevertheless, as the anaesthetist was always the same and unaware of the group allocation, this approach seemed justified to detect differences between the two groups. An objective scoring system to evaluate the plane of anaesthesia could have been used to make these results more reliable (Enderle et al. 2008; Gozalo-Marcilla et al. 2013).

Recoveries from general anaesthesia were better and more successful at the first attempt in horses receiving dexmedetomidine compared with those treated with medetomidine. An improvement in recovery quality was also seen when comparing dexmedetomidine with saline (Marcilla et al. 2012). Better recoveries with dexmedetomidine may be the result of a shorter sedative and muscle relaxant effect in comparison to medetomidine (Grimsrud et al. 2012; Rezende et al. 2015). Nevertheless, it has to be kept in mind, that the horses of group DEX received additional post sedation in 4 cases, whereas this was only necessary in 1 horse in group MED, which might reduce the direct comparability of the two groups in regards to recovery quality.

This study may have been impaired by two major limitations. First, the non-objective way of assessing anaesthetic depth, which probably prevented us from detecting slight differences in isoflurane requirements between groups. Furthermore, the exclusion of the blood gas variables of ten horses with  $\text{PaO}_2 < 80 \text{ mmHg}$  (10.7 kPa) where inspired oxygen fraction had to be increased, which led to a reduced number of data for statistical analysis.

In conclusion, dexmedetomidine at 50% dose of medetomidine was not equisedative to medetomidine in horses. Dose rates to reach intended sedation before induction of anaesthesia were more individually variable with dexmedetomidine than with medetomidine. Cardiopulmonary function during general anaesthesia was almost identical and within

324 clinically accepted ranges in both groups. Recoveries from general anaesthesia were of better  
325 quality in horses receiving dexmedetomidine, without any differences in recovery related  
326 times.

327

328   **References**

- 329   Bettschart-Wolfensberger R, Bettschart RW, Vainio O et al. (1999a) Cardiopulmonary effects  
330       of a two hour medetomidine infusion and its antagonism by atipamezole in horses and  
331       ponies. *J vet Anaesth* 26, 8–12
- 332   Bettschart-Wolfensberger R, Clarke KW, Vainio O et al. (1999b) Pharmacokinetics of  
333       medetomidine in ponies and elaboration of a medetomidine infusion regime which  
334       provides a constant level of sedation. *Res Vet Sci* 67, 41–46.
- 335   Bettschart-Wolfensberger R, Dicht S, Vullo C et al. (2011) A clinical study on the effect in  
336       horses during medetomidine-isoflurane anaesthesia, of butorphanol constant rate  
337       infusion on isoflurane requirements, on cardiopulmonary function and on recovery  
338       characteristics. *Vet Anaesth Analg* 38, 186–194.
- 339   Bettschart-Wolfensberger R, Freeman SL, Bowen IM et al. (2005) Cardiopulmonary effects  
340       and pharmacokinetics of i.v. dexmedetomidine in ponies. *Equine Vet J* 37, 60–64.
- 341   Bettschart-Wolfensberger R, Jäggin-Schmucker N, Lendl C et al. (2001) Minimal alveolar  
342       concentration of desflurane in combination with an infusion of medetomidine for the  
343       anaesthesia of ponies. *Vet Rec* 148, 264–267.
- 344   Bettschart-Wolfensberger R, Larenza P (2007) Balanced anaesthesia in the equine. *Clin Tech*  
345       *Eq Pract* 6, 104–110.
- 346   Carroll CL, Huntington PJ (1988) Body condition scoring and weight estimation of horses.  
347       *Equine Vet J* 20, 41–45.
- 348   Devisscher L, Schauvliege S, Dewulf J et al. (2010) Romifidine as a constant rate infusion in  
349       isoflurane anaesthetized horses: a clinical study. *Vet Anaesth Analg* 37, 425–433.
- 350   Enderle AK, Levionnois OL, Kuhn M et al. (2008) Clinical evaluation of ketamine and  
351       lidocaine intravenous infusions to reduce isoflurane requirements in horses under  
352       general anaesthesia. *Vet Anaesth Analg* 35, 297–305.

- 353 Gozalo-Marcilla M, Gasthuys F, Schauvliege S (2014) Partial intravenous anaesthesia in the  
354 horse: a review of intravenous agents used to supplement equine inhalation  
355 anaesthesia. Part 1: lidocaine and ketamine. *Vet Anaesth Analg* 41, 335–345.
- 356 Gozalo-Marcilla M, Gasthuys F, Schauvliege S (2015) Partial intravenous anaesthesia in the  
357 horse: a review of intravenous agents used to supplement equine inhalation  
358 anaesthesia. Part 2: opioids and alpha-2 adrenoceptor agonists. *Vet Anaesth Analg*  
359 42, 1–16.
- 360 Gozalo-Marcilla M, Steblaj B, Schauvliege S et al. (2013) Comparison of the influence of two  
361 different constant-rate infusions (dexmedetomidine versus morphine) on anaesthetic  
362 requirements, cardiopulmonary function and recovery quality in isoflurane  
363 anaesthetized horses. *Res Vet Sci* 95, 1186–1194.
- 364 Granholm M, McKusick BC, Westerholm FC et al. (2007) Evaluation of the clinical efficacy  
365 and safety of intramuscular and intravenous doses of dexmedetomidine and  
366 medetomidine in dogs and their reversal with atipamezole. *Vet Rec* 160, 891–897.
- 367 Grimsrud KN, Mama KR, Steffey EP et al. (2012) Pharmacokinetics and pharmacodynamics  
368 of intravenous medetomidine in the horse. *Vet Anaesth Analg* 39, 38–48.
- 369 Kalchofner KS, Picek S, Ringer SK et al. (2009) A study of cardiovascular function under  
370 controlled and spontaneous ventilation in isoflurane-medetomidine anaesthetized  
371 horses. *Vet Anaesth Analg* 36, 426–435.
- 372 Kalchofner KS, Ringer SK, Boller J et al. (2006) Clinical assessment of anesthesia with  
373 isoflurane and medetomidine in 300 equidae. *Pferdeheilkunde* 22, 301–308
- 374 Kästner SB, Von Rechenberg B, Keller K et al. (2001) Comparison of medetomidine and  
375 dexmedetomidine as premedication in isoflurane anaesthesia for orthopaedic surgery  
376 in domestic sheep. *J Vet Med A* 48, 231–241.



- 377 Kuusela E, Raekallio M, Anttila M et al. (2000) Clinical effects and pharmacokinetics of  
378 medetomidine and its enantiomers in dogs. *J Vet Pharmacol Ther* 23, 15–20.
- 379 Marcilla MG, Schauvliege S, Segaert S et al. (2012) Influence of a constant rate infusion of  
380 dexmedetomidine on cardiopulmonary function and recovery quality in isoflurane  
381 anaesthetized horses. *Vet Anaesth Analg* 39, 49–58.
- 382 Marly-Voquer C, Schwarzwald CC, Bettschart-Wolfensberger R (2016) The use of  
383 dexmedetomidine continuous rate infusion for horses undergoing transvenous  
384 electrical cardioversion – A case series. *Can Vet J* 57, 70–75.
- 385 Pöppel N, Hopster K, Geburek F et al. (2015) Influence of ketamine or xylazine  
386 supplementation on isoflurane anaesthetized horses-a controlled clinical trial. *Vet*  
387 *Anaesth Analg* 42, 30–38.
- 388 Ranheim B, Risberg AI, Spadavecchia C et al. (2015) The pharmacokinetics of  
389 dexmedetomidine administered as a constant rate infusion in horses. *J Vet Pharmacol*  
390 *Ther* 38, 93–96.
- 391 Raszplewicz J, MacFarlane P, West E (2013) Comparison of sedation scores and propofol  
392 induction doses in dogs after intramuscular premedication with butorphanol and either  
393 dexmedetomidine or medetomidine. *Vet Anaesth Analg* 40, 584–589.
- 394 Rezende ML, Grimsrud KN, Stanley SD et al. (2015) Pharmacokinetics and  
395 pharmacodynamics of intravenous dexmedetomidine in the horse. *J Vet Pharmacol*  
396 *Ther* 38, 15–23.
- 397 Ringer SK, Kalchofner K, Boller J et al. (2007) A clinical comparison of two anaesthetic  
398 protocols using lidocaine or medetomidine in horses. *Vet Anaesth Analg* 34, 257–268.
- 399 Schauvliege S, Marcilla MG, Verryken K et al. (2011) Effects of a constant rate infusion of  
400 detomidine on cardiovascular function, isoflurane requirements and recovery quality  
401 in horses. *Vet Anaesth Analg* 38, 544–554.

402 Taylor P, Coumbe K, Henson F et al. (2014) Evaluation of sedation for standing clinical  
403 procedures in horses using detomidine combined with buprenorphine. *Vet Anaesth*  
404 *Analg* 41, 14–24.

405 Vettorato E, Chase-Topping ME, Clutton RE (2010) A comparison of four systems for  
406 scoring recovery quality after general anaesthesia in horses. *Equine Vet J* 42, 400–4

407 Virtanen R, Savola JM, Saano V et al. (1988) Characterization of the selectivity, specificity  
408 and potency of medetomidine as an alpha2-adrenoceptor agonist. *Eur J Pharmacol*,  
409 150 9–14.

410 Yamashita K, Tsubakishita S, Futaok S et al. (2000) Cardiovascular effects of medetomidine,  
411 detomidine and xylazine in horses. *J Vet Med Sci* 62, 1025–1032.

412  
413  
414  
415

**Figure 1** Flow diagram of the progress representing number of horses analysed during sedation, general anaesthesia and recovery. Reasons for exclusions are given in brackets. For sedation prior to induction, number of horses receiving additional sedative boli (termed *top-up*) necessary to fulfil sedation criteria is given. Numbers of horses receiving additional post sedation for recovery (DEX: 1  $\mu\text{g kg}^{-1}$ ; MED: 2  $\mu\text{g kg}^{-1}$ ) are listed at the bottom. IV, intravenously; *n*, number of horses;  $\text{FIO}_2$ , fraction of inspired oxygen

**Figure 2** Heart rates (HR) and mean arterial blood pressures (MAP) in horses during dexmedetomidine isoflurane (group DEX) or medetomidine isoflurane (group MED) balanced anaesthesia (mean  $\pm$  SD). Significant time points are marked with \*. Represented on the x-axis are minutes after anaesthesia induction and number of horses per group; nD, number of horses in group DEX; nM, number of horses in group MED (reductions due to different durations of anaesthesia)

**Figure 3** Recovery scores in horses following dexmedetomidine isoflurane (group DEX) or medetomidine isoflurane (group MED) balanced anaesthesia. Groups differed significantly ( $p = 0.042$ )

432 **Table 1** Criteria used to assess depth of sedation (adapted from Taylor et al. 2014;  
433 *Evaluation of sedation for standing clinical procedures in horses using detomidine combined*  
434 *with buprenorphine*)

---

**Sedation criteria**

---

- 1 Head height lower than withers (eyes as bench mark)
- 2 Lower lip atonic
- 3 No reaction to stimulation with a pen, when touching the inside of the ears

---

435

436 **Table 2** Scoring system used to assess recovery from anaesthesia

Score awarded	Description of recovery
1	Very good, standing at the first attempt
2	Good, two attempts until standing
3	More than two attempts, horse remains calm, minimal ataxia when standing
4	Bad, several attempts to get up, horse becomes excited or in panic, risk of injury
5	Very bad, recovery resulting in injury of the horse

438

439 **Table 3** Mean  $\pm$  SD of venous and arterial blood gas values, ratio of arterial partial pressure

440 of oxygen to fraction of inspired oxygen ( $\text{PaO}_2/\text{FIO}_2$ ), pH, arterial lactate concentrations

441 (Lac), total haemoglobin (Hb), arterial base excess (BE) and electrolytes in horses with

442 dexmedetomidine isoflurane (group DEX) or medetomidine isoflurane (group MED)

443 balanced anaesthesia. Significant differences ( $p < 0.05$ ) between groups are indicated by \*

444 and significant changes over time are indicated with #

	t <sub>30</sub>	t <sub>60</sub>	t <sub>90</sub>	t <sub>150</sub>	Significant differences, <i>p</i> -value
Venous PCO <sub>2</sub> Dex (mmHg)	49.50±5.5	52.11±4.1	53.05±5.4	55.33±6.2	#, <i>p</i> < 0.001
Venous PCO <sub>2</sub> Med	51.68±3.0	52.59±4.6	53.60±4.7	55.13±5.5	
Venous PCO <sub>2</sub> Dex (kPa)	6.4±0.7	6.8±0.5	6.9±0.7	7.2±0.8	
Venous PCO <sub>2</sub> Med	6.7±0.4	6.8±0.6	7.0±0.6	7.2±0.7	
Venous PO <sub>2</sub> Dex <sup>#</sup> (mmHg)	45.33±7.8	49.52±7.0	51.54±8.3	49.17±6.6	#, <i>p</i> < 0.001
Venous PO <sub>2</sub> Med <sup>#</sup>	48.95±6.8	52.48±6.5	53.47±7.1	56.49±9.1	
Venous PO <sub>2</sub> Dex <sup>#</sup> (kPa)	5.9±1.0	6.4±0.9	6.7±1.1	6.4±0.9	
Venous PO <sub>2</sub> Med <sup>#</sup>	6.4±0.9	6.8±0.8	7.0±0.9	7.3±1.2	
Arterial PCO <sub>2</sub> Dex <sup>#</sup> (mmHg)	47.98±4.8	50.13±4.3	51.44±4.7	52.92±3.1	#, <i>p</i> < 0.001
Venous PCO <sub>2</sub> Med <sup>#</sup>	48.73±4.56	50.83±4.5	51.8±4.6	53.57±5.6	
Venous PCO <sub>2</sub> Dex <sup>#</sup> (kPa)	6.2±0.6	6.5±0.6	6.7±0.6	6.9±0.4	
Venous PCO <sub>2</sub> Med <sup>#</sup>	6.3±0.6	6.6±0.6	6.7±0.6	7.0±0.7	
Arterial PO <sub>2</sub> Dex <sup>#</sup> (mmHg)	159.70±53.49	154.01±49.39	154.95±51.01	146.43±33.14	#, <i>p</i> = 0.005
Venous PCOMed <sup>#</sup>	153.03±42.95	146.14±43.58	147.16±40.90	161.15±24.04	
Venous PCODex <sup>#</sup> (kPa)	20.8±7	20.0±6.4	20.1±6.6	19.0±4.3	
Venous PCOMed <sup>#</sup>	19.9±5.6	19±5.7	19.1±5.3	20.9±3.1	
PaO <sub>2</sub> /FIO <sub>2</sub> Dex <sup>#</sup>	314±102	301±92	304±100	289±59	#, <i>p</i> = 0.003
PaO <sub>2</sub> /FIO <sub>2</sub> Med <sup>#</sup>	304±93	288±83	295±85	291±78	
pH Dex <sup>#</sup>	7.37±0.03	7.36±0.03	7.36±0.03	7.37±0.03	#, <i>p</i> < 0.001
pH Med	7.38±0.04	7.36±0.03	7.37±0.04	7.37±0.04	
Lac Dex <sup>#</sup>	1.36±0.31	1.59±0.38	1.59±0.39	1.65±0.64	
Lac Med	1.43±0.41	1.71±0.39	1.69±0.42	1.57±0.31	
Hb Dex <sup>#</sup>	11.59±1.32	11.08±1.20	10.69±1.50	10.49±1.41	* t <sub>150</sub> , <i>p</i> = 0.02
Hb Med	12.11±1.72	11.78±1.65	11.59±1.79	12.16±2.17	#, <i>p</i> < 0.001
BE Dex <sup>#</sup>	1.73±2.07	1.98±2.01	2.70±1.91	4.32±1.6	#, <i>p</i> < 0.001
BE Med	2.21±2.14	2.23±2.25	3.25±1.95	4.41±2.42	
Electrolytes					
Na <sup>+</sup> Dex	133.2±1.64	133.75±1.72	134.05±1.83	134.67±2.55	#, <i>p</i> = 0.001
Na <sup>+</sup> Med	130±2.10	134.83±2.43	135.23±2.34	135.71±2.85	
K <sup>+</sup> Dex	3.52±0.24	3.44±0.24	3.45±0.28	3.50±0.37	
Na <sup>+</sup> Med	3.54±0.22	3.51±0.27	3.48±0.21	3.52±0.28	
Ca <sup>++</sup> Dex	1.40±0.06	1.37±0.05	1.35±0.05	1.33±0.05	#, <i>p</i> < 0.001
Na <sup>+</sup> Med	1.43±0.06	1.40±0.07	1.39±0.07	1.36±0.09	
Cl <sup>-</sup> Dex	98.86±2.71	99.03±1.87	99.40±2.18	99.5±3	
Na <sup>+</sup> Med	99.21±2.3	99.55±2.18	99.38±2.29	99.54±2.9	

- 446 PaO<sub>2</sub>, PaCO<sub>2</sub>/PvO<sub>2</sub>, PvCO<sub>2</sub>, arterial and venous oxygen and carbon dioxide partial pressures; Lac, arterial lactate concentration (mmol L<sup>-1</sup>); Hb, total
- 447 hemoglobine g dL<sup>-1</sup>; BE, arterial base excess (mmol L<sup>-1</sup>); Na<sup>+</sup>, ionised sodium (mmol L<sup>-1</sup>); K<sup>+</sup>, ionised potassium (mmol L<sup>-1</sup>); Ca<sup>++</sup>, ionised calcium (mmol L<sup>-1</sup>);
- 448 Cl<sup>-</sup>, ionised chloride (mmol L<sup>-1</sup>)



